REMARKS

Status of the claims

Claims 1-9 are pending in the application. The amendment to claim 1 adds no new matter.

For convenience, the rejections will be addressed in the order presented in the Office Action mailed December 19, 2003.

Amendment to the specification

The amendment to the specification adds no new matter; it removes the embedded hyperlink as required by the Examiner.

Rejections under 35 U.S.C. § 103--Birkenmeyer and Livak

Claims 1, 2, 4, 5, and 9 were rejected as allegedly unpatentable over Birkenmeyer, *et al.*, U.S. Patent No. 5,453,355 ("Birkenmeyer") in view of Livak, *et al.*, U.S. Patent No. 5,538,848 ("Livak"). The Examiner argues that it would have been *prima facie* obvious to use a probe taught by Livak (labeled with a fluorescent dye and a quencher) in the method described by Birkenmeyer in order to obtain real-time quantification. Applicants respectfully traverse.

As the Examiner knows, in order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria. First, the prior art reference or combination of references must teach or suggest all of the claim elements. Second, the Examiner must show that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Third, the Examiner must show that there is a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. The Examiner's arguments fail to meet these criteria.

The invention is drawn to a real-time amplification reaction that employs a dual-labeled probe. The amplification reaction takes place in the presence of the probe, which hybridizes to the entire sequence between the primer binding site. Birkenmeyer teaches amplification reactions and probes for the detection of the amplified products, which probes span the sequence between primer binding sites and overlap into the primer binding sites. However, Birkenmeyer does not teach concurrent probe hybridization and amplification. The probe hybridization steps described in Birkenmeyer take place after the amplification reaction (*see, e.g.,* column 6, lines 23-29; column 7, lines 23-43; column 9, lines 12-25).

Livak teaches an amplification using a dual-labeled probe and a polymerase having 5' to 3' exonuclease activity. However, Livak does not teach a probe that hybridizes to all of the nucleotides between the primer binding sites and in some embodiments, extends into the primer binding site. Moreover, in Livak, the probe is included as a component of the amplification reaction (*see, e.g.,* column 3, lines 29-47). Accordingly, hybridization of probes and primers occurs concurrently in the same reaction mixture.

The Examiner contends that one of skill would have been motivated to combine the teachings of Birkenmeyer and Livak in order to quantify the reaction. Thus, according to the Examiner, a practitioner would have been motivated to double-label the Birkenmeyer probe and use it during amplification with the various primer sets. However, the rejection provides no evidence or reasoning as to why one of skill would expect the modified reaction comprising the primers and probe taught by Birkenmeyer would work. Accordingly, the Examiner has failed to establish a proper case of *prima facie* obviousness.

Applicants submit herewith a Rule 1.132 Declaration by Dr. Christoph Kessler to provide additional evidence that the requisite reasonable expectation of success is lacking. According to Dr. Kessler, based on the teachings in the cited art, it would not have been reasonable for one of skill in the art to conclude that the probe and primers described by Birkenmeyer, modified and used in accordance with Livak, could be successfully employed in a homogeneous amplification reaction..

As Dr. Kessler explains, in the method described by Livak, the probe hybridizes to the amplified product during the amplification reaction. As the primers are extended,

polymerase encounters the hybridized probe and degrades it via the polymerase 5 to 3" exonuclease activity, thus generating a signal. In the current invention, the probe binds to all of the nucleotides between the primer binding sites. In some embodiments, the probe extends directly from the end of the forward primer site into the reverse primer binding site. The polymerase must therefore be able to extend the primers without interference from the adjacent and/or overlapping probe. Further, the polymerase must be able to degrade the probe without interference from the adjacent and/or overlapping primers. Dr. Kessler indicates that a practitioner of ordinary skill in the art would predict that the primers and probe would interfere with one another, thus compromising the quantitative amplification reaction. Thus, there would not have been a reasonable expectation of success that the combination of references would result in the claimed invention.

Dr. Kessler further explains that in Birkenmeyer, only primer sets 5, 7, and 9 are shown to result in amplicon products smaller than 100 bp (*see, e.g.,* Figure 2). In these cases the primers sets markedly overlap with the probe (SEQ ID NO:8, position 892-937 as set forth at column 6, line 43; positions 894-936 in Table 1). In particular, the forward primers (SEQ ID NOs 4 and 6) are fully included in the probe. Use of the probe and primers concurrently would results in hybridization between primer and probe, thus preventing binding of the primer to the target DNA and thereby inhibiting amplicon formation.

In addition, Dr. Kessler notes that the 5' terminus of the probe, which is required for 5'nuclease degradation in the assay described by Livak, is at a position that falls upstream of the amplicon region in all cases. Therefore, the disclosed probe could not be used in a homogeneous assay, as Taq DNA polymerase could not degrade the 5'-terminus during amplification.

Last, in paragraph 8 of the Declaration, Dr. Kessler explains that the primer set designated "13" in Example 5 (which describes a "short" PCR product) cannot be used in a homogeneous assay because the 3' end of each primer terminates at a position immediately adjacent to the 3' end of the other primer. Therefore, there is no sequence between both primers for internal binding of a probe that is degraded during primer elongation because of the inhibiting overlap with the opposite primer.

Dr. Kessler concludes that a practitioner of ordinary skill in the art would not have considered the primers and probes described in Birkenmeyer to be useful for quantification methods in a homogeneous format as taught by Livak.

With regard to claim 2, as the Examiner acknowledges, Birkenmeyer does not explicitly disclose probes that hybridize to the complete sequence between primer binding site, but don't overlap into one or more of the primer binding sites. However, such probes are not taught by Livak. Thus, the references do not disclose all of the elements of claim 2.

The Examiner argues that claimed probes (claim 2) could be readily derived from Birkenmeyer. First, the rejection cites to passages in Birkenmeyer that indicate that a probe binds to a sequence of DNA lying between the oligonucleotide primers used for amplification and that any DNA sequence found between each primer of a primer pair may be suitable for use (*see,* the Office Action at page 4). Next, the Examiner points to the primer set forth in SEQ ID NO:5, which has a 2 bp overlap with the probe (SEQ ID NO:8), and argues that a practitioner would omit the 2 bp overlap to optimize conditions and that it would be further to omit the 2 bps because they are inconsequential to primer function. (*See*, Office Action page 5, referring to *Ex parte Wu* 10 USP1 2031 (Bd. Pat. App. & Inter. 1989) "The courts have stated that it would be obvious to omit an element when a function attributed to said element is not desired or required."). She concludes that in view of the general teaching that the probe should bind to sequences between the primer binding sites and the desirability of achieving the benefits of a rapid, sensitive, and reproducible method of detection of *Neiserria gonorrhoeae,* it would have been obvious to modify SEQ ID NO:5 of Birkenmeyer so that it does not overlap with the probe. Applicants disagree.

The Examiner has not established that all of the elements are suggested by the references. The Examiner's suggestion that omitting the overlap in SEQ ID NO:5 would optimize the method, or that it is routine to omit 2 bp from a primer sequence and achieve the same result, is merely conclusory. The rejection fails to point to a principle known in the art that would lead one of skill to the specific modification to SEQ ID NO:5 suggested by the Examiner.

Further, the holding in *Ex Parte Wu* is in applicable here, as Birkenmeyer attributes no function to the 2' overhang. In *Ex Parte Wu*, the court held that the prior art specifically taught under what conditions inclusion of the element under discussion would be desirable, and concluded that where those conditions did not exist, it would be obvious to eliminate the element as being superfluous. Here, Birkenmeyer is silent as to the reason why the 2 bp overhang is present in the cited embodiment, and thus provides no basis of judging the desirability of keeping or eliminating the 2 bp overhang. Thus, the Examiner's argument fails to support a proper case of *prima facie* obviousness.

Claims 4 and 9 depend from claim 1 and are therefore also unobvious for the reasons set forth above.

In view of the foregoing, the claims are patentable over the cited art. Applicant therefore respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 103--Birkenmeyer and Greisen

Claims 3 and 6-8 were rejected as unpatentable over Birkenmeyer and Greisen *et al.* (*J. Clin. Microbiol.* 32:335-351, 1994) ("Griesen"). The Examiner alleges that Greisen teaches non-specific primers and probes and that it would have been obvious to use the primers and probes in the method of Birkenmeyer. Applicants respectfully traverse.

The art cited in this rejection does not provide all of the elements of the claims. In particular, neither Griesen nor Birkenmeyer teach a dual labeled probe that is present in the amplification reaction. The rejection therefore does not establish a *prima facie* case of obviousness.

Furthermore, even if the Examiner had cited Livak in conjunction with Birkenmeyer and Greisen, the combination of Livak and Birkenmeyer does not arrive at the claimed invention for the reasons described above. The teachings of Griesen do not cure this defect. Accordingly, the claims are unobvious. Applicants therefore respectfully request withdrawal of the rejection.

Obviousness-type double patenting rejections

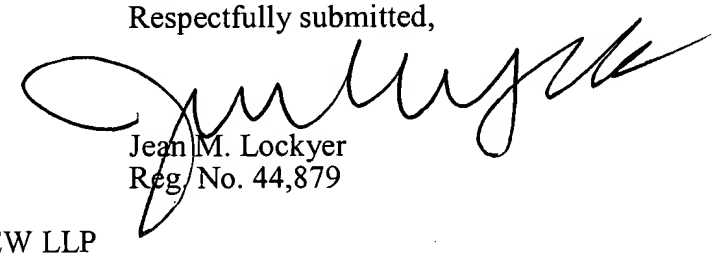
Claims 1-9 were provisionally rejected for obviousness-type double patenting as being unpatentable over claims 1, 4, 5, 8, and 11-14 of co-pending Application No. 09/530,929. The instant application and the '929 application are commonly owned. Claims 1-9 were also rejected for obviousness-type double patenting over a second application. Although the rejection in part 4 refers to Application No. 09/530,929, the arguments presented in the section refer to Application No. 09/530,736. This application is also commonly owned. According to MPEP § 822.01, "[i]f the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent..." The cited applications are not currently allowed. Accordingly, if these rejections become the only outstanding rejections, the present claims should be allowed. However, if one or both of the above-listed applications is allowed in the interim, Applicant will gladly consider providing a terminal disclaimer as necessary.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.5088
Kessler	Examiner: Sally A. Sakelaris
Application No.: 09/530,747	Art Unit: 1634
Filed: October 23, 2000	DECLARATION UNDER 37 C.F.R. § 1.132 BY CHRISTOPH KESSLER, Ph.D.
For: SPECIFIC AND SENSITIVE NUCLEIC ACID DETECTION METHOD	
Customer No.: 20350	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Christoph Kessler, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I currently hold the position of Director of Molecular Systems at Roche Diagnostics GMbH. I have been at Roche Diagnostics GmbH since 1997 and at Boehringer Mannheim since 1980. I am also an associate professor since 1990 at the University of Munich, Gene Center and Institute of Biochemistry, in the field of molecular biology and nucleic acid analytics. I received a Ph.D. from at the University of Erlangen and Munich, where I studied chemistry and biochemistry from 1976-1979. I have been continuously working in the field of molecular biology and research and development of molecular diagnostic techniques since 1980.

3. I am a named inventor on the above-referenced patent application and have read and am familiar with its contents. The invention provides a method of detecting a nucleic acid using a homogeneous assay format. The method employs amplification primers, a dual-labeled probe that comprises a region that is essentially complementary to all of the sequence that is between the primer binding sites, and an enzyme having 5' exonuclease activity. The amplified sequences are short, *e.g.*, 75 nucleotides or less in length.

4. I have reviewed the Office Action mailed December 19, 2003. It is my understanding that the Examiner believes that the claims are obvious in view of US Patent No. 5,453,355 to Birkenmeyer, *et al.* ("Birkenmeyer") and US Patent No. 5,538,848 to Livak, *et al.* ("Livak"). The Examiner describes Birkenmeyer as teaching specific primer pairs that produce amplificates with a length less than 61 nucleotides, and an internal probe that binds to all of the nucleotides between the primer binding sites and overlaps into the primer binding sites. The rejection asserts that it would have been obvious to use a dual-labeled reporter molecule taught by Livak as the internal probe in the method of Birkenmeyer because it would have been desirable to perform real-time quantification. This declaration explains that one of skill in the art would not have predicted that the probe disclosed by Birkenmeyer, modified and used in accordance with Livak, could be successfully employed in homogeneous amplification reactions employing the primers described by Birkenmeyer.

5. In the real-time PCR method disclosed by Livak, the probe hybridizes to the amplified product during the amplification reaction. As the primers are extended, polymerase encounters the hybridized probe and degrades it via the polymerase 5' exonuclease activity, thus generating a signal. In the current invention, the probe binds to all of the nucleotides between the primer binding sites and in some embodiments overlaps into the primer binding site. The polymerase must therefore be able to extend the primers without interference from the probe. Further, the polymerase must be able to degrade the probe without interference from the primers. The probes disclosed in Birkenmeyer span the region between the primers and overlap into the primer binding site. A practitioner in the art would expect the probe to interfere with efficient primer binding and extension and thus compromise the amplification reaction.

6. In Birkenmeyer, only primer sets 5, 7, and 9 are shown to result in amplicon products smaller than 100 bp (*see, e.g.,* Figure 2). In these cases the primers sets markedly overlap with the probe (SEQ ID NO:8, position 892-937 as set forth at column 6, line 43; positions 894-936 in Table 1). In particular, the forward primers (SEQ ID NOs 4 and 6) are fully included in the probe. Use of the primers and probe concurrently results in hybridization between primer and probe, thus preventing binding of the primer to the target DNA and thereby inhibiting amplicon formation.

7. In addition, the 5' terminus of the probe, which is required for 5'nuclease degradiation, is at a position that falls upstream of the amplicon region in all cases. Therefore, the disclosed probe could not be used in a homogeneous assay, as Taq DNA polymerase could not degrade the 5'-terminus during amplification.

8. Furthermore, the primer set designated "13" in Example 5 (which describes a "short" PCR product) cannot be used in a homogeneous assay because the 3' end of each primer terminates at a position immediately adjacent to the 3' end of the other primer. Therefore, there is no sequence between both primers for internal binding of a probe that is degraded during primer elongation because of the inhibiting overlap with the opposite primer.

9. In summary, a practitioner of ordinary skill in the art would not have concluded that the primers and probes described in Birkenmeyer would be useful for quantification methods in a homogeneous format as taught by Livak.

Dated: June-17/2004 By: Christoph Kessler
Christoph Kessler, Ph.D.

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